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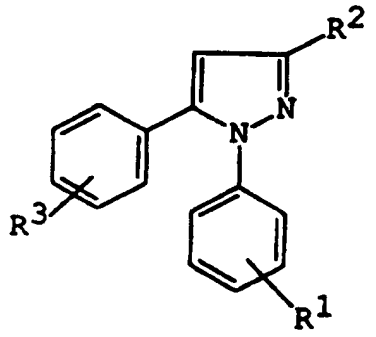
(54) Title: 1,3,5-TRISUBSTITUTED PYRAZOLES FOR TREAMENT OF INFLAMMATION

(57) Abstract

A compound of the formula (I) wherein R^1 is hydroxyethyl, 1-hydroxy-1-methylethyl, hydrogen, halogen, nitro, or cyano, R^2 is chloro, cyano, or lower alkyl optionally substituted with halogen, and R^3 is lower alkylthio, lower alkylsulfinyl, or lower alkylsulfonyl, provided that when R^1 is hydrogen, halogen, nitro, or cyano, then R^2 is chloro, and a pharmaceutically acceptable salt thereof, processes for their preparation and pharmaceutical compositions.



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DESCRIPTION

1,3,5-TRISUBSTITUTED PYRAZOLES FOR TREATMENT OF INFLAMMATION

This invention relates to novel pyrazole compounds having pharmacological activity, to a process for their production and to a pharmaceutical composition containing the same.

More particularly, it relates to novel pyrazole compounds, which have pharmaceutical activity such as inhibiting activity of cyclooxygenase-2 (hereinafter described as COX-II), to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

Accordingly, one object of this invention is to provide the novel pyrazole compounds, which have an inhibiting activity of COX-II.

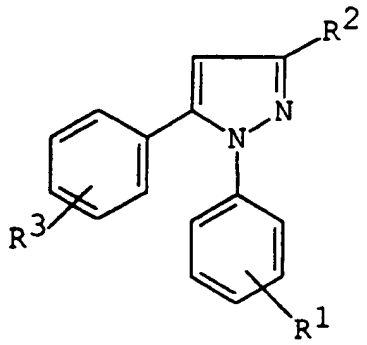
Another object of this invention is to provide a process for production of the pyrazole compounds.

A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the pyrazole compounds.

Still further object of this invention is to provide a use of the pyrazole compounds for manufacturing a medicament for treating or preventing various diseases.

Some pyrazole derivatives having antiinflammatory and analgesic activities have been known as described, for example, in Canadian Patent 1 130 808, and EP Patent Publication Nos. 248 594, 272 704, 293 220, 418 845 and 554 829, and WO Patent Publication Nos. 95/15315, 95/15316, 95/15317 and 95/15318.

The object pyrazole derivatives of this invention are new and can be represented by the following general formula [I].

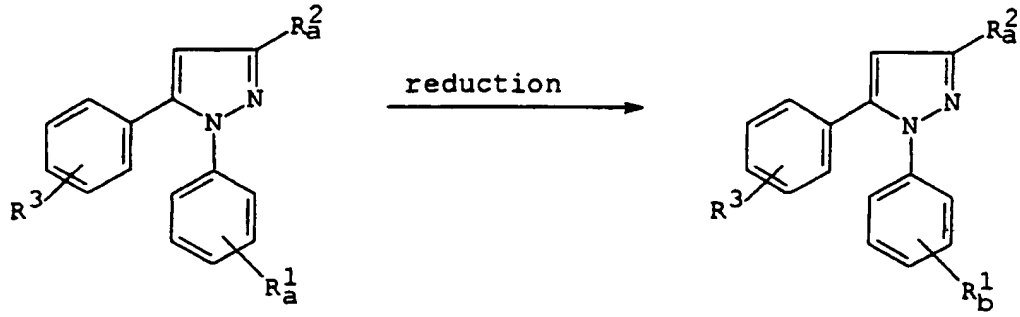


[I]

wherein R^1 is hydroxyethyl, 1-hydroxy-1-methylethyl, hydrogen, halogen, nitro, or cyano,
R^2 is chloro, cyano, or lower alkyl optionally substituted with halogen, and
R^3 is lower alkylthio, lower alkylsulfinyl, or lower alkylsulfonyl,
provided that when R^1 is hydrogen, halogen, nitro, or cyano,
then R^2 is chloro,
and a pharmaceutically acceptable salt thereof.

The object compound [I] or a salt thereof can be prepared by the following processes.

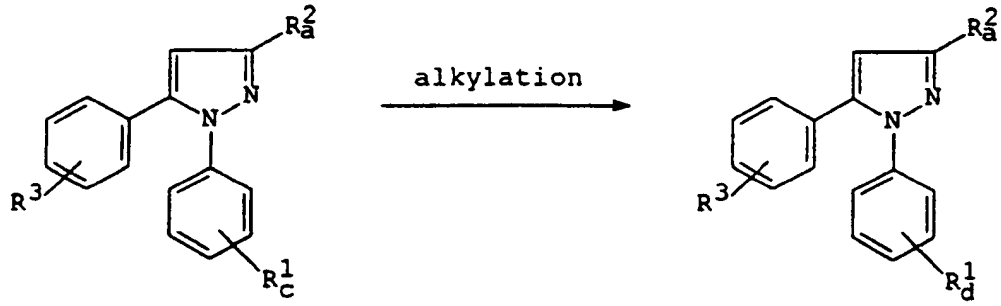
Process 1



[II]
or a salt thereof

[Ia]
or a salt thereof

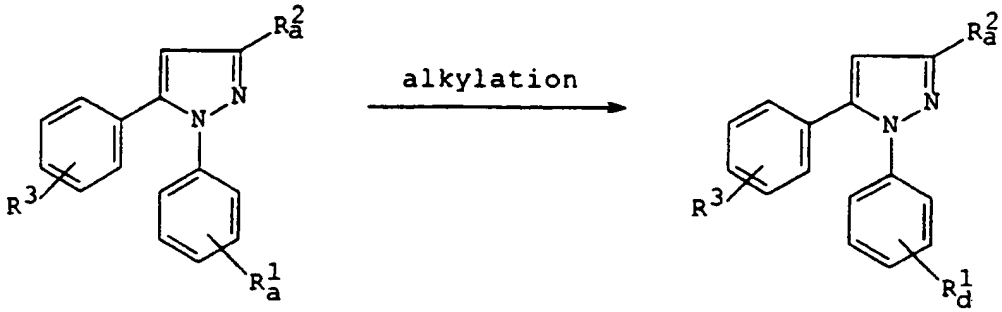
Process 2



[III]
or its reactive derivative
at the carboxy group,
or a salt thereof

[Ib]
or a salt thereof

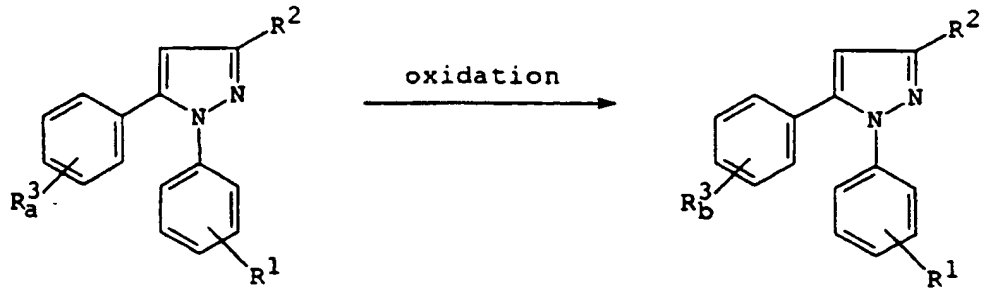
Process 3



[II]
or a salt thereof

[Ic]
or a salt thereof

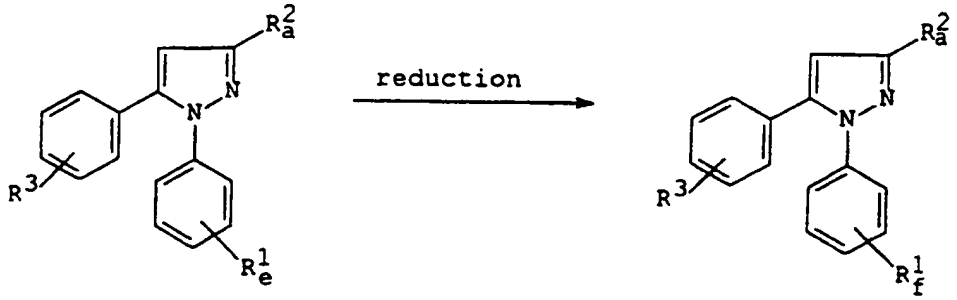
Process 4



[Id]
or a salt thereof

[Ie]
or a salt thereof

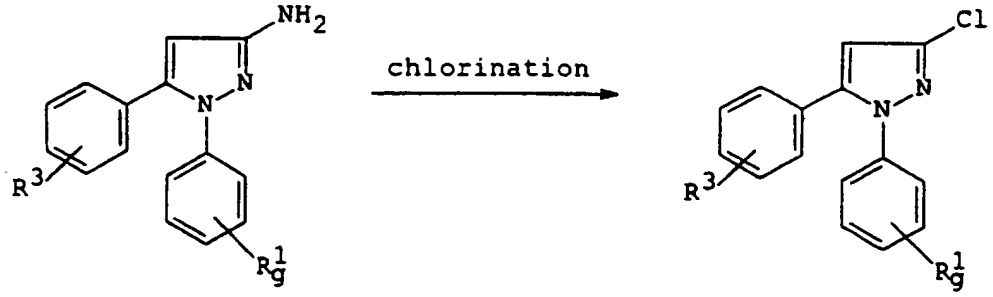
Process 5



[IV]
or its reactive derivative at the carboxy group, or a salt thereof

[If]
or a salt thereof

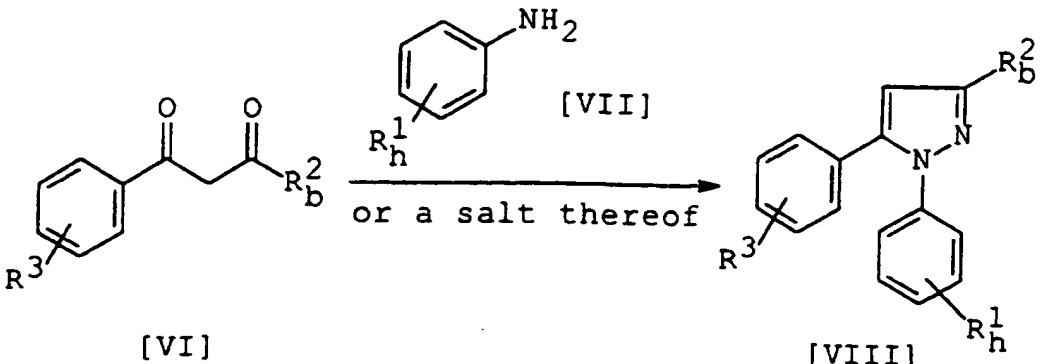
Process 6



[V]
or a salt thereof

[Ig]
or a salt thereof

Referential Process



[VI]
or a salt thereof

[VIII]
or a salt thereof

wherein R^1, R^2 and R^3 are each as defined above,

R^1_a is acetyl,
R^1_b is 1-hydroxyethyl,
R^1_c is carboxy,
R^1_d is 1-hydroxy-1-methylethyl,
R^1_e is carboxymethyl,
R^1_f is 2-hydroxyethyl,
R^1_g is hydrogen, halogen, nitro or cyano,
R^1_h is lower alkanoyl, hydroxyethyl, 1-hydroxy-1-methylethyl, hydrogen, halogen, nitro, or cyano,
R^2_a is cyano or lower alkyl optionally substituted with halogen,
R^2_b is halogen, cyano, or lower alkyl optionally substituted with halogen,
R^3_a is lower alkylthio, and
R^3_b is lower alkylsulfinyl or lower alkylsulfonyl.

In the above and subsequent description of the present specification, suitable examples of the various definitions

to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

The term "hydroxyethyl" is intended to mean 1-hydroxyethyl or 2-hydroxyethyl.

Suitable "lower alkyl" and lower alkyl moiety in the terms "lower alkylthio", "lower alkylsulfinyl" and "lower alkylsulfonyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like, in which preferable one is methyl.

Suitable "lower alkylthio" may be methylthio, ethylthio, propylthio, and the like, in which preferable one is methylthio.

Suitable "lower alkylsulfinyl" may be methylsulfinyl, ethylsulfinyl, propylsulfinyl, and the like, in which preferable one is methylsulfinyl.

Suitable "lower alkylsulfonyl" may be methylsulfonyl, ethylsulfonyl, propylsulfonyl, and the like, in which preferable one is methylsulfonyl.

Suitable "halogen" may be fluoro, chloro, bromo and iodo.

Suitable "lower alkyl substituted with halogen" may be difluoromethyl, trifluoromethyl, and the like.

Suitable "lower alkanoyl" may be formyl, acetyl, propionyl, butyryl, isobutyryl, and the like.

Suitable pharmaceutically acceptable salts of the compounds [I] are conventional non-toxic salts and include an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic acid addition salt [e.g. hydrochloride, hydrobromide,

sulfate, phosphate, etc.], a salt with an amino acid [e.g. aspartic acid salt, glutamic acid salt, etc.], and the like.

The compounds [I] and pharmaceutically acceptable salt according to present invention may contain one or more asymmetric centers, and thus they can exist as enantiomers or diastereoisomers, and the invention includes both mixtures and separate individual isomers.

The compound [I] and pharmaceutically acceptable salt thereof according to the present invention can be in the form of a solvate, which was included within the scope of the present invention. The solvate preferably includes a hydrate, an ethanolate, and so on.

Also included in the scope of invention are radiolabelled derivatives of compounds [I] which are suitable for biological studies.

Process 1

The compound [Ia] or a salt thereof can be prepared by reacting a compound [II] or a salt thereof with a reducing agent.

Suitable reducing agent may be diborane, sodium borohydride, lithium aluminum hydride, and the like.

The reaction is usually carried out in a conventional solvent such as diethyl ether, tetrahydrofuran, or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Process 2

The compound [Ib] or a salt thereof can be prepared by reacting a compound [III] or its reactive derivative at the carboxy group, or a salt thereof with alkylating reagent.

Suitable reactive derivative at the carboxy group of

the compound [III] may include an ester, an acid anhydride and the like. The suitable examples of the reactive derivatives may be a symmetrical acid anhydride; a mixed acid anhydride with 1,1'-carbonyl diimidazole or an acid such as aliphatic acid [e.g. acetic acid, pivalic acid, etc.], substituted phosphoric acid [e.g. dialkylphosphoric acid, diphenylphosphoric acid, etc.]; an ester such as lower alkyl ester [e.g. methyl ester, ethyl ester, propyl ester, hexyl ester, etc.], substituted or unsubstituted ar(lower)alkyl ester [e.g. benzyl ester, p-chlorobenzyl ester, etc.], substituted or unsubstituted aryl ester [e.g. phenyl ester, tolyl ester, 4-nitrophenyl ester, 2,4-dinitrophenyl ester, pentachlorophenyl ester, naphthyl ester, etc.], or an ester with N,N-dimethylhydroxylamine, N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxy-6-chloro-1H-benzotriazole, or the like.

Suitable alkylating reagent may be organometallic compound such as alkyl lithium (e.g. methyl lithium, ethyl lithium, etc.), alkyl magnesium halide (e.g. methyl magnesium bromide, ethyl magnesium bromide, etc.) and so on.

The reaction is usually carried out in a conventional solvent such as diethyl ether, tetrahydrofuran, or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried under cooling to heating.

Process 3

The compound [Ic] or a salt thereof can be prepared by reacting a compound [II] or a salt thereof, with alkylating reagent.

This reaction can be carried out in substantially the same manner as that of Process 2, and therefore the

reaction mode and reaction conditions [e.g. reagent solvent, reaction temperature, etc.] of this reaction are to be referred to those explained in Process 2.

Process 4

The compound [Ie] or a salt thereof can be prepared by reacting a compound [Id] or a salt thereof with an oxidizing agent.

The suitable oxidizing agent may be hydrogen peroxide, cumene hydroperoxide, tert-butyl hydroperoxide, Jones reagent, peracid [e.g. peracetic acid, perbenzoic acid, m-chloroperbenzoic acid, monopersulfate compound (oxone ®), etc.], chromic acid, potassium permanganate, alkali metal periodate [e.g. sodium periodate, etc.], and the like.

This reaction is usually carried out in a solvent which does not adversely influence the reaction such as acetic acid, dichloromethane, acetone, ethyl acetate, chloroform, water, an alcohol [e.g. methanol, ethanol, etc.], a mixture thereof or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 5

The compound [If] or a salt thereof can be prepared by reacting a compound [IV] or its reactive derivative at the carboxy group, or a salt thereof with a reducing agent.

Suitable reducing agent may be diborane, sodium borohydride, lithium aluminum hydride, and the like. When a chiral reducing reagent, such as a combination of borane and (R) or (S)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine, is used, a chiral compound [If] is obtained.

The reaction is usually carried out in a conventional solvent such as diethyl ether, tetrahydrofuran, or any

other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Process 6

The compound [Ig] or a salt thereof can be prepared by the following methods.

Namely, 1) the compound [V] or a salt thereof is firstly reacted with a nitrite compound, and then 2) the resulting product is reacted with cuprous chloride.

Suitable nitrite compound may be alkali metal nitrite [e.g. sodium nitrite, potassium nitrite, etc.], alkyl nitrite [e.g. isoamyl nitrate, tert-butyl nitrite, etc.], and the like.

In the first step, the reaction is preferably carried out in the presence of an acid [e.g. hydrochloric acid sulfuric acid, etc.].

The reaction is usually carried out in a solvent such as water, tetrahydrofuran, dioxane, acetonitrile, or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction temperature is not critical and the reaction can be carried out under cooling to warming.

In the second step, the reaction is preferably carried out in the presence of alkali metal halide [e.g. sodium chloride, etc.] and an inorganic acid [e.g. hydrochloric acid, etc.].

The reaction is usually carried out in a solvent such as water, tetrahydrofuran, dioxane, or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction temperature is not critical and the reaction can be carried out warming to heating.

Referential Process

The compound [VIII] or a salt thereof, which includes some of the compound [I] and the starting compounds usable for its preparation processes, can be prepared from the compound [VI] or a salt thereof and the compound [VII] or a salt thereof by the following method.

First the compound [VII] can be converted to the corresponding hydrazine derivatives by reacting with metal nitrite (e.g. sodium nitrite, etc.) and reducing agent (e.g. tin chloride, etc.) under the acidic condition. Then the hydrazine derivatives can be reacted with the compound [VI] to give the compound [VIII].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

Suitable salts of the compound [Ia] to [Ig], [II], [V], [VI], [VII] and [VIII] may be the same as those exemplified for the compound [I].

Suitable salts of the compound [III] and [IV] are an alkalimetal salt [e.g. sodium salt, potassium salt, etc.], an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], and the like.

The object compound [I] or pharmaceutically acceptable

salts thereof possesses inhibiting activity of COX-II and possesses strong antiinflammatory, analgesic, antithrombotic, anti-cancer activities and so on. The object compound [I] and pharmaceutically acceptable salts thereof, therefore, are useful for the treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals, and more particularly for the treatment and/or prevention of inflammation and pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.], inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.], inflammatory eye condition [e.g. conjunctivitis, etc.], lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.], condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.], gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, particularly those in which lipoxygenase and cyclooxygenase products are a factor, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodosa, rheumatic fever, Sjögren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimer's disease, and the like. Additionally, the object compound [I] or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular

diseases, the diseases caused by hyperglycemia and hyperlipemia.

In order to illustrate the usefulness of the object compound [I], the pharmacological test data of the compound [I] are shown in the following.

[A] ANTIINFLAMMATORY ACTIVITY :

Effect on adjuvant arthritis in rats :

(i) Test Method :

Ten female Sprague-Dawley rats were used per group. A dose of 0.5 mg of Mycobacterium tuberculosis (strain M37 BA) suspended in 0.05 ml of liquid paraffin was injected subcutaneously in the right hind paw. The injection of mycobacterial adjuvant produced local inflammatory lesions (primary lesion) and then about 10 days later, secondary lesions in both the injected and uninjected paws. The volumes of both paws before and on days 23 after the injection was measured as percent inhibition in comparison to vehicle-treated controls. The drug was given orally once a day for 23 consecutive days from day 1 after the injection.

(ii) Test Results :

Test compound (Example No.)	Dose (mg/kg)	Inhibition of secondary lesion (uninjected paw) (%)
12	3.2	≧95
13-2)	3.2	≧95
Ibuprofen	100	79.6

[B] ANALGESIC ACTIVITY :

Inflammatory hyperalgesia induced by brewer's yeast in rats :

(i) Test Method :

Ten male Sprague Dawley rats were used per group. 0.1 ml of 5% brewer's yeast suspended in 0.5% methylcellulose was injected into the right hind paw. The pain threshold was determined 3 hours after yeast injection, by applying pressure to the foot and reading the pressure at which the rat withdrew the foot.

The drugs were given orally 2 hours after yeast injection. The pain threshold in the treated animals was compared with that in the control animals.

(ii) Test Results :

Test compound (Example No.)	Dose (mg/kg)	Relative potency (Control = 1.0)
1	10	$\geq$1.4

[C] COX-I and COX-II activity in vitro :

(i) Test Method :

a. Preparation of the recombinant cyclooxygenase (COX)

The human cyclooxygenase COX-I and COX-II were expressed in transfected Chinese hamster ovary (CHO) cells. Monolayer cultures of semi-confluent CHO cells stably expressing COX-I and COX-II were washed twice and scraped into phosphate buffered saline (PBS). The cells were centrifuged at 200 x g for 5 minutes and the cell pellet was sonicated in reaction buffer containing 100 mM Tris-HCl

(pH 7.4), 2 μM hematin and 5 mM tryptophan. Broken cells were centrifuged for 5 minutes at 1700 x g at 4°C and the supernatants were used as crude enzymes.

Cyclooxygenase activities in the absence or presence of inhibitors were measured by determining the level of prostaglandin E_2 (PGE_2) synthesis from arachidonic acid. Enzymes (1 μg for COX-I and/or 3 μg for COX-II) in a total volume of 200 μl of reaction buffer were incubated in the absence and presence of various concentrations of inhibitors for 5 minutes at 30°C. The reaction was then started by the addition of arachidonic acid to the final concentration of 10 μM. The reaction was terminated by 50 μl of HCl (1N) after incubation at 30°C for 5 minutes. PGE_2 was extracted with ethyl acetate, concentrated under a stream of nitrogen and analyzed by a radio immunoassay kit (Amersham) according to the manufacture's instructions.

b. Assay for human recombinant COX-I and COX-II activity

COX activity was assayed as PGE_2 formation using radioimmunoassay to detect the prostaglandin release. The appropriate COX enzyme was incubated in 0.1 M Tris-HCl buffer (pH 7.3) containing hematin and tryptophan with the addition of arachidonic acid (10 μM) for 5 minutes at 37°C. Compounds were pre-incubated with the enzyme for 5 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after 5 minutes at 37°C by addition of 20 μl of 1N HCl. PGE_2 formation was measured by radioimmunoassay (Amersham).

(ii) Test Results :

Test compound (Example No.)	Human COX-II IC_{50} (μM)	Human COX-I IC_{50} (μM)
13-2)	<0.1	≧60

[D] Toxicities of Compound (I)

Test on the toxicity by repetitive oral administration of the compound disclosed in Example 13-2) in SD rat was conducted, and the dead at dose of 32 mg/kg once a day for 14 consecutive days could not be observed.

For therapeutic purpose, the compound [I] and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external (topical) administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the compound [I] will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound [I] may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

(1) A mixture of ethyl 1-(4-acetylphenyl)-5-[4-(methylthio)phenyl]pyrazole-3-carboxylate (6.4 g) and sodium methoxide (2.6 g) in N,N-dimethylformamide (60 ml) was stirred at 100°C for 1.5 hours. The resulting mixture was poured into water (200 ml). The resulting precipitates were collected by filtration, washed with water and dried in vacuo to give 1-(4-acetylphenyl)-5-[4-(methylthio)phenyl]pyrazole-3-carboxamide (5.0 g).

mp : 112-115°C

IR (Nujol) : 3400, 1680, 1600, 1200 cm^{-1}

(2) A solution of phosphorous oxychloride (2.78 ml) in N,N-dimethylformamide (60 ml) was stirred at 0°C for 30 minutes. To this solution, 1-(4-acetylphenyl)-5-[4-(methylthio)phenyl]pyrazole-3-carboxamide (5.0 g) was added at one portion. After being stirred for additional 30 minutes, the resulting mixture was poured into a mixture of ice-water (100 ml). The resulting precipitates were collected by filtration, washed with water and dried in vacuo to give 1-(4-acetylphenyl)-5-[4-(methylthio)phenyl]-pyrazole-3-carbonitrile (3.76 g).

mp : 124-125°C

IR (Nujol) : 2250, 1690, 1680, 1510 cm^{-1}

Preparation 2

A mixture of 4-aminoacetophenone (10 g) and sodium nitrite (5.1 g) in acetic acid (55 ml) was stirred at 10°C for 1 hour. To the resulting mixture were added concentrated hydrochloric acid (25 ml) and stannous

chloride dihydrate (41 g), and stirred at 0°C for 30 minutes. To the reaction mixture was added 1-[4-(methylthio)phenyl]butane-1,3-dione (15.4 g), and stirred at ambient temperature for 1 hour. The mixture was stirred at 100°C for 3 hours and poured into ice-water. The resulting precipitates were filtered, washed with water, and dried under reduced pressure to give 1-(4-acetylphenyl)-3-methyl-5-[4-(methylthio)phenyl]pyrazole (24.6 g).

IR (Nujol) : 1680, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.28 (3H, s), 2.47 (3H, s), 2.57 (3H, s), 6.48 (1H, s), 7.16 (2H, d, J=8.5Hz), 7.25 (2H, d, J=8.5Hz), 7.36 (2H, d, J=8.6Hz), 7.96 (2H, d, J=8.6Hz)

MASS (m/z) : 323 (M+1)

Preparation 3

(1) To a mixture of 1-(4-acetylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (7.85 g) and perchloric acid (70%, 23.6 ml) in the mixture of 1,4-dioxane (40 ml) and methanol (120 ml) was added thallium(III) nitrate trihydrate (14.32 g), and stirred at ambient temperature overnight. The resultant mixture was added to water (140 ml), extracted with toluene, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and toluene (1:5) to give crystals of methyl 4-[5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazol-1-yl]phenylacetate (4.66 g).

mp : 136-138°C

IR (Nujol) : 1735, 1605, 1310, 1230 cm^{-1}

NMR ($CDCl_3$, δ) : 3.08 (3H, s), 3.67 (2H, s), 3.71 (3H, s), 6.84 (1H, s), 7.10-8.00 (8H, m)

MASS (m/z) : 439 (M+1)

(2) The mixture of methyl 4-[5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazol-1-yl]phenylacetate (1.00 g) and 1N-sodium hydroxide (5 ml) in the solution of tetrahydrofuran (5 ml) and methanol (10 ml) was stirred at ambient temperature for 1 hour. The resultant mixture was acidified with hydrochloric acid. The precipitates were filtered and washed with water. The filtrate was recrystallized from ethanol to give crystals of 4-[5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazol-1-yl]phenylacetic acid (0.75 g).

mp : 184-186°C

IR (Nujol) : 1710, 1605, 1305, 1235 cm^{-1}

NMR ($CDCl_3$, δ) : 3.09 (3H, s), 3.71 (2H, s), 6.85 (1H, s), 7.27 (2H, d, J=8.7Hz), 7.35 (2H, d, J=8.7Hz), 7.44 (2H, d, J=8.5Hz), 7.92 (2H, d, J=8.5Hz)

MASS (m/z) : 425 (M+1)

Elemental Analysis Calcd. for $C_{19}H_{15}F_3N_2O_4S$: C 53.77, H 3.56, N 6.60

Found : C 53.44, H 3.38, N 6.36

Preparation 4

(1) 4-Chlorophenylhydrazine hydrochloride (4.0 g) was added to a solution of sodium (0.5 g) in ethanol (50 ml), and the mixture was refluxed for 1 hour. To the cooled mixture was added 3-[4-(methylthio)phenyl]acrylonitrile (3.0 g), and the resulting mixture was refluxed overnight. Ethyl acetate and water were added to the reaction mixture. The organic layer was separated, dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30 g) eluting with a mixture of toluene and ethyl acetate (9:1) to give 1-(4-chlorophenyl)-5-[4-(methylthio)phenyl]-2-pyrazolin-3-amine (3.4 g).

NMR (DMSO-d_6, δ) : 2.44 (3H, s), 2.50 (1H, dd,

J=16.4, 5.7Hz), 3.44 (1H, dd, J=16.4, 10.8Hz), 4.98 (1H, dd, J=10.8, 5.7Hz), 5.84 (2H, br s), 6.62 (2H, d, J=9.0Hz), 7.02 (2H, d, J=9.0Hz), 7.02 (4H, s)

MASS (m/z) : 318 (M+1)

(2) A mixture of 1-(4-chlorophenyl)-5-[4-(methylthio)-phenyl]-2-pyrazoline-3-amine (3.4 g) and manganese(IV) oxide (2.7 g) in dichloromethane (500 ml) was stirred at ambient temperature for 2 hours. The insoluble material was filtered and the filtrate was concentrated to dryness. The residue was purified by column chromatography on silica gel eluting with a mixture of toluene and ethyl acetate (4:1) to give 1-(4-chlorophenyl)-5-[4-(methylthio)phenyl]pyrazole-3-amine (0.82 g).

NMR (DMSO-d_6, δ) : 2.47 (3H, s), 5.02 (2H, br s), 5.83 (1H, s), 7.14 (4H, d, J=9Hz), 7.24 (2H, d, J=9Hz), 7.38 (2H, d, J=9Hz)

MASS (m/z) : 316 (M+1)

Preparation 5

(1) 5-[4-(Methylthio)phenyl]-1-phenyl-2-pyrazoline-3-amine was prepared from 3-[4-(methylthio)phenyl]-acrylonitrile in a similar manner to that of Preparation 4-(1).

NMR (DMSO-d_6, δ) : 2.44 (3H, s), 2.48 (1H, dd, J=16, 6Hz), 3.41 (1H, dd, J=16, 10Hz), 4.93 (1H, dd, J=10, 6Hz), 5.73 (2H, br s), 6.49 (1H, t, J=7Hz), 6.65 (2H, d, J=8Hz), 7.00 (2H, dd, J=7, 8Hz), 7.22 (4H, s)

MASS (m/z) : 284 (M+1)

(2) 5-[4-(Methylthio)phenyl]-1-phenylpyrazole-3-amine was prepared from 5-[4-(methylthio)phenyl]-1-phenyl-2-pyrazoline-3-amine in a similar manner to that of

Preparation 4-(2).

NMR (DMSO-d_6, δ) : 2.46 (3H, s), 4.95 (2H, br s), 5.82 (1H, s), 7.09-7.36 (9H, complex m.)

MASS (m/z) : 282 (M+1)

Preparation 6

A solution of 5-[4-(methylthio)phenyl]-1-(4-nitrophenyl)pyrazole-3-carboxylic acid (4.8 g) in thionyl chloride (50 ml) was refluxed for 3 hours and concentrated under reduced pressure. A solution of the residue in tetrahydrofuran (50 ml) was added dropwise to a solution of sodium azide (1.1 g) in the mixture of acetone (40 ml) and water (20 ml) at 0°C. The mixture was stirred for 1 hour and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give an oil (5.1 g). A solution of the oil (5.1 g) in N,N-dimethylformamide (50 ml) was stirred at 100° to 110°C for 2 hours and concentrated under reduced pressure. The residue was triturated in a mixture of diisopropyl ether and ethyl ether to give a powder (4.2 g). The mixture of an above powder (4.2 g) and concentrated hydrochloric acid (70 ml) was refluxed for 3 hours and cooled to 0°C. The reaction mixture was adjusted to pH=10 with an aqueous sodium hydroxide and extracted with a mixture of ethyl acetate and tetrahydrofuran. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (250 g) eluting with a mixture of acetone and dichloromethane (1:10) to give a yellow powder of 5-[4-(methylthio)phenyl]-1-(4-nitrophenyl)pyrazole-3-amine (2.1 g).

mp : 195-196°C

IR (Nujol) : 3400, 3320, 1515, 1330 cm^{-1}

NMR ($CDCl_3$, δ) : 2.51 (3H, s), 5.94 (1H, s), 7.15

(2H, d, J=8.7Hz), 7.23 (2H, d, J=8.7Hz), 7.38 (2H, d, J=9.2Hz), 8.13 (2H, d, J=9.2Hz)

MASS (m/z) : 327 (M+1)

Preparation 7

A solution of 1-(4-cyanophenyl)-5-[4-(methylthio) phenyl]pyrazole-3-carboxylic acid (2 g) in thionyl chloride (20 ml) was refluxed for 3 hours and concentrated under reduced pressure. A solution of the above residue in tetrahydrofuran (20 ml) was added dropwise to a mixture of sodium azide (0.7 g) and sodium bicarbonate (0.5 g) in a mixture of acetone (20 ml) and water (10 ml) at 0°C. The mixture was stirred for 1 hour and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The solution of the residue in N,N-dimethylformamide (20 ml) was stirred at 100° to 110°C for 1 hour and poured into a mixture of ice and water. The resultant precipitates were collected, washed with water, and dried under reduced pressure. The mixture of the products and concentrated hydrochloric acid (40 ml) was refluxed for 4 hours and adjusted to pH=10 with an aqueous sodium hydroxide. The reaction mixture was extracted with a solution of ethyl acetate and tetrahydrofuran. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (150 g) eluting with a mixture of methanol and chloroform (1:10) to give 4-[5-[4-(methylthio)phenyl]-3-aminopyrazol-1-yl]benzoic acid (0.75 g).

IR (Nujol) : 1605, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 2.46 (3H, s), 4.95 (2H, br s), 5.83 (1H, s), 7.04 (2H, d, J=8.3Hz), 7.12 (2H, d, J=8.3Hz), 7.21 (2H, d, J=8.3Hz), 7.78 (2H, d, J=8.3Hz)

MASS (m/z) : 326 (M+1)

Preparation 8

(1) To a solution of 4-aminoacetophenone (5.42 g) in acetic acid (42 ml) was added sodium nitrite (2.95 g) at room temperature. After stirring for 30 minutes, hydrochloric acid (16.8 ml) was added to the mixture at 5°C and the resultant mixture was stirred for 20 minutes. Tin chloride dihydrate (23.28 g) was added by portions for 30 minutes at 5°C and the resultant mixture was stirred for 20 minutes at the same temperature. 1-[4-(Methylthio)phenyl]-4,4-difluoro-1,3-dioxobutane (7.0 g) was added at 25°C and the mixture was stirred for 1 hour at 45°C. To the mixture was added water (182 ml) at 20°C. After stirring for 1 hour, the resulting precipitate was collected by filtration and washed with water. After drying at 40°C in vacuo overnight, to a solution of the crude product in acetone (103 ml) was added water (67 ml) dropwise. After stirring at 20°C for 1 hour, the resultant precipitate was collected by filtration, and washed with the mixture of acetone and water (3:2, 31 ml) and dried at 40°C in vacuo overnight to give 1-(4-acetylphenyl)-3-difluoromethyl-5-[4-(methylthio)-phenyl]pyrazole (8.63 g).

(2) A mixture of 1-(4-acetylphenyl)-3-difluoromethyl-5-(4-methylthiophenyl)pyrazole (8.5 g), tetrabutylammonium hydrogensulfate (1.61 g), oxone® (30.58 g : $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$), ethyl acetate (128 ml) and water (85 ml) was heated under reflux for 2 hours. To the reaction mixture was added water and ethyl acetate. Organic layer was separated and washed with brine and dried over magnesium sulfate. After removing magnesium sulfate by filtration, the filtrate was concentrated under reduced pressure. After dissolving the residue by adding ethyl acetate at 40°C, the resultant solution was allowed to cool

to room temperature. Then the solution was stirred for an hour with ice-bath cooling. The resulting precipitate was collected by filtration and washed with cold ethyl acetate (13 ml) and dried at 40°C in vacuo overnight to give crude crystals (6.67 g).

The obtained crude crystals (6.50 g) was dissolved in 90% aqueous ethanol (91 ml; ethanol 82 ml and water 9 ml) at 75°C. After stirring for 30 minutes, the filtrate was cooled gradually at 65°C and then seed crystals were added. The temperature of the mixture was cooled to 60°C and was maintained in the range of 55-60°C for 30 minutes. After cooling to 25°C over a period of 1 hour, the temperature was kept in the range of 25-30°C for more than an hour. The resultant precipitate was collected by filtration, washed with ethanol and dried in vacuo at 40°C for more than an hour to give 1-(4-acetylphenyl)-3-difluoromethyl-5-[4-(methylsulfonyl)phenyl]pyrazole (5.85 g).

mp : 145-152°C

IR (Nujol) : 1682, 1602, 1314, 1154 cm^{-1}

NMR ($CDCl_3$, δ) : 2.63 (3H, s), 3.09 (3H, s), 6.80 (1H t, J=54.7Hz), 6.85 (1H, s), 7.38 (2H, d, J=8.7Hz), 7.44 (2H, d, J=8.5Hz), 7.94 (2H, d, J=8.5Hz), 7.99 (2H, d, J=8.7Hz)

MASS (m/z) : 391 $(M+H)^+$

Example 1

To a stirred solution of 1-(4-acetylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (0.72 g) in methanol (7 ml), sodium borohydride (80 mg) was added portionwise at 15°C. The resulting mixture was stirred for 1 hour at ambient temperature, treated with acetic acid (1 ml) and then concentrated under reduced pressure. To the residue, a mixture of ethyl acetate and water was added, and stirred. The organic layer was separated, washed with an aqueous solution of sodium bicarbonate and subsequently

brine. The solution was dried over magnesium sulfate and concentrated under reduced pressure. The residual oil was crystallized with toluene and filtered to give crystals of 1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (0.54 g).

mp : 138-140°C

IR (Nujol) : 3500, 1605, 1500, 1300 cm^{-1}

NMR (DMSO-d_6, δ) : 1.33 (3H, d, J=6Hz), 3.26 (3H, s), 4.77 (1H, m), 5.32 (1H, br d, J=4Hz), 7.33 (2H, d, J=8Hz), 7.35 (1H, s), 7.45 (2H, d, J=8Hz), 7.57 (2H, d, J=8Hz), 7.93 (2H, d, J=8Hz)

MASS (m/z) : 411 (M^{+1}), 393 (M^{+1}-18)

Example 2

The following compounds described in (1) to (4) were obtained according to a similar manner to that of Example 1.

(1) 1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole

mp : 98-99°C

IR (Nujol) : 3450, 1605, 1500, 1270, 1230 cm^{-1}

NMR ($CDCl_3$, δ) : 1.49 (3H, d, J=6Hz), 1.72 (1H, br s), 2.48 (3H, s), 4.93 (1H, q, J=6Hz), 6.72 (1H, s), 7.12 (2H, d, J=9Hz), 7.18 (2H, d, J=9Hz), 7.29 (2H, d, J=9Hz), 7.38 (2H, d, J=9Hz)

MASS (m/z) : 379 (M^{+1})

(2) 3-Difluoromethyl-1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 144-146°C

IR (Nujol) : 3400, 1600, 1310, 1150 cm^{-1}

NMR ($CDCl_3$, δ) : 1.50 (3H, d, J=6Hz), 2.05 (1H, br s), 3.08 (3H, s), 4.95 (1H, q, J=6Hz), 6.78 (1H, t, J=5.5Hz), 6.83 (1H, s), 7.25 (2H, d, J=8Hz),

7.41 (2H, d, J=8Hz), 7.44 (2H, d, J=9Hz), 7.89 (2H, d, J=9Hz)

MASS (m/z) : 393 (M^{+1}), 375 (M^{+1}-18)

(3) 1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylthio)phenyl]-pyrazole-3-carbonitrile

pale yellow oil

IR (Film) : 3450, 2250, 1605, 1510, 1480 cm^{-1}

(4) 1-[4-(1-Hydroxyethyl)phenyl]-3-methyl-5-[4-(methylthio)phenyl]pyrazole

IR (Nujol) : 3250, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.32 (3H, d, J=6Hz), 2.25 (3H, s), 2.46 (3H, s), 4.73 (1H, m), 5.24 (1H, d, J=4Hz), 6.40 (1H, s), 7.12 (2H, d, J=8Hz), 7.17 (2H, d, J=8Hz), 7.21 (2H, d, J=8Hz), 7.35 (2H, d, J=8Hz)

MASS (m/z) : 325 (M+1)

Example 3

To a stirred solution of 4-[5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazol-1-yl]benzoic acid (18 g) in ether (100 ml), a solution of methyl lithium in ether (1.2N solution: 130 ml) was slowly added at ambient temperature. The resulting mixture was refluxed for 1.5 hours and then cooled. The reaction mixture was quenched with an aqueous saturated solution of ammonium chloride and extracted with ethyl acetate several times. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give an oil. This oil was crystallized with isopropyl ether to give 1-(4-acetylphenyl)-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole (8.5 g).

mp : 138-140°C

IR (Nujol) : 1690, 1600, 1270, 1240 cm^{-1}

NMR ($CDCl_3$, δ) : 2.49 (3H, s), 2.62 (3H, s), 6.75 (1H, s), 7.12 (2H, d, J=9Hz), 7.20 (2H, d, J=9Hz), 7.43 (2H, d, J=9Hz), 7.96 (2H, d, J=9Hz)

The following compound was obtained as a by-product.

1-[4-(1-Hydroxy-1-methylethyl)phenyl]-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole

Yellow oil

IR (Nujol) : 3400, 1600, 1500, 1470, 1440, 1230 cm^{-1}

NMR ($CDCl_3$, δ) : 1.57 (3H, s), 1.58 (3H, s), 2.48 (3H, s), 6.72 (1H, s), 7.13 (2H, d, J=9Hz), 7.18 (2H, d, J=9Hz), 7.24 (2H, d, J=9Hz), 7.49 (2H, d, J=9Hz)

MASS (m/z) : 393 (M^{+1})

Example 4

A mixture of 1-[4-(1-hydroxy-1-methylethyl)phenyl]-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole (1.1 g) and m-chloroperbenzoic acid (0.55 g) in dichloromethane (30 ml) was stirred at 5°C for 30 minutes. The resulting mixture was washed with an aqueous saturated solution of sodium bicarbonate and subsequently brine. The solution was dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel and eluted with dichloromethane. The fractions containing object compound were combined and concentrated under reduced pressure to give an amorphous powder. This powder was washed with n-hexane to give 1-[4-(1-hydroxy-1-methylethyl)phenyl]-5-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)pyrazole (0.54 g).

IR (Neat) : 3400, 1600, 1500, 1470, 1440 cm^{-1}

NMR ($CDCl_3$, δ) : 1.59 (6H, s), 2.76 (3H, s), 6.81

(1H, s), 7.26 (2H, d, J=9Hz), 7.40 (2H, d, J=8Hz), 7.51 (2H, d, J=9Hz), 7.62 (2H, d, J=8Hz)

MASS (m/z) : 409 (M^{+1}), 391 (M^{+1}-18)

Example 5

A mixture of 1-[4-(1-hydroxy-1-methylethyl)phenyl]-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole (1.5 g) and m-chloroperbenzoic acid (1.45 g) in dichloromethane (35 ml) was stirred at ambient temperature for one hour. The resulting mixture was washed with an aqueous saturated solution of sodium bicarbonate and subsequently brine. The organic solution was dried over magnesium sulfate and concentrated under reduced pressure. The residual oil was subjected to column chromatography on silica gel and eluted with a mixture of toluene and ethyl acetate. The fractions containing object compound were combined and concentrated under reduced pressure to give a white powder. This powder was crystallized with a mixture of ethanol and water to give 1-[4-(1-hydroxy-1-methylethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (0.52 g).

mp : 147-148°C

IR (Nujol) : 3550, 1610, 1500, 1410 cm^{-1}

NMR ($CDCl_3$, δ) : 1.60 (6H, s), 3.09 (3H, s), 6.85 (1H, s), 7.26 (2H, d, J=9Hz), 7.45 (2H, d, J=8Hz), 7.53 (2H, d, J=9Hz), 7.91 (2H, d, J=8Hz)

MASS (m/z) : 425 (M^{+1})

Example 6

To a solution of 1-(4-acetylphenyl)-3-methyl-5-[4-(methylthio)phenyl]pyrazole (2.0 g) in tetrahydrofuran (50 ml) was added a 1N-solution (31 ml) of methylmagnesium bromide in tetrahydrofuran, and stirred for 5 hours at 0°C. To the resultant mixture was added water, extracted with ethyl acetate, washed with brine, dried over magnesium

sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of toluene and ethyl acetate (5:1) to give 1-[4-(1-hydroxy-1-methylethyl)phenyl]-3-methyl-5-[4-(methylthio)phenyl]pyrazole (0.64 g).

NMR (DMSO-d_6, δ) : 1.42 (6H, s), 2.25 (3H, s), 2.46 (3H, s), 5.09 (1H, s), 6.40 (1H, s), 7.13 (2H, d, J=8.7Hz), 7.15 (2H, d, J=8.6Hz), 7.21 (2H, d, J=8.7Hz), 7.46 (2H, d, J=8.6Hz)

MASS (m/z) : 339 (M+1)

Example 7

The following compounds described in (1) to (4) were obtained according to a similar manner to that of Example 4.

(1) 1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylsulfinyl)-phenyl]-3-(trifluoromethyl)pyrazole
amorphous powder

IR (Neat) : 1610, 1500, 1470, 1400 cm^{1}

NMR ($CDCl_3$, δ) : 1.50 (3H, d, J=6Hz), 2.75 (3H, s), 4.95 (1H, q, J=6Hz), 6.82 (1H, s), 7.28 (2H, d, J=8Hz), 7.40 (2H, d, J=9Hz), 7.40 (2H, d, J=8Hz), 7.62 (2H, d, J=9Hz)

MASS (m/z) : 377 (M^{+1}-18)

(2) 1-[4-(1-Hydroxyethyl)phenyl]-3-methyl-5-[4-(methylsulfinyl)phenyl]pyrazole

IR ($CHCl_3$) : 3350, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 1.32 (3H, d, J=6.4Hz), 2.28 (3H, s), 2.76 (3H, s), 4.74 (1H, qd, J=6.4, 4.4Hz), 5.24 (1H, d, J=4.4Hz), 6.53 (1H, s), 7.18 (2H, d, J=8.4Hz), 7.36 (2H, d, J=8.4Hz), 7.40 (2H, d, J=8.4Hz), 7.65 (2H, d, J=8.4Hz)

MASS (m/z) : 341 (M+1)

(3) 1-[4-(1-Hydroxy-1-methylethyl)phenyl]-3-methyl-5-[4-(methylsulfinyl)phenyl]pyrazole

mp : 121-122°C

NMR (DMSO-d_6, δ) : 1.42 (6H, s), 2.28 (3H, s), 2.76 (3H, s), 5.10 (1H, s), 6.53 (1H, s), 7.16 (2H, d, J=8.5Hz), 7.40 (2H, d, J=8.3Hz), 7.48 (2H, d, J=8.5Hz), 7.65 (2H, d, J=8.3Hz)

MASS (m/z) : 355 (M+1)

(4) 1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylsulfinyl)-phenyl]pyrazole-3-carbonitrile

amorphous powder

IR (Neat) : 3400, 2280, 1600, 1510 cm^{-1}

NMR ($CDCl_3$, δ) : 1.51 (3H, d, J=7Hz), 2.15 (1H, d, J=4Hz), 2.75 (3H, s), 4.95 (1H, dd, J=7, 4Hz), 6.93 (1H, s), 7.25 (2H, d, J=4Hz), 7.37 (2H, d, J=9Hz), 7.42 (2H, d, J=9Hz), 7.63 (2H, d, J=9Hz)

MASS (m/z) : 352 (M^{+1}), 334 (M^{+1}-18)

Example 8

1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile was prepared from the 1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylthio)phenyl]pyrazole-3-carbonitrile in a similar manner to that of Example 5.

mp : 112-113°C

IR (Nujol) : 3350, 2250, 1510, 1310 cm^{-1}

NMR ($CDCl_3$, δ) : 1.52 (3H, d, J=6Hz), 1.97 (1H, br s), 3.08 (3H, s), 4.97 (1H, q, J=6Hz), 6.97 (1H, s), 7.25 (2H, d, J=9Hz), 7.42 (2H, d, J=8Hz), 7.44 (2H, d, J=9Hz), 7.92 (2H, d, J=8Hz)

MASS (m/z) : 368 (M^{+1}), 350 (M^{+1}-18)

Example 9

To the mixture of 4-[5-[4-(methylsulfonyl)phenyl]-3-

(trifluoromethyl)pyrazol-1-yl]phenylacetic acid (1.00 g) in tetrahydrofuran (10 ml) was added dropwise the 1M solution of borane in tetrahydrofuran (5 ml), and stirred at ambient temperature overnight. The several drops of acetic acid was added to the resultant mixture. The mixture was concentrated under reduced pressure and water was added to the resultant. The mixture was extracted with ethyl acetate, washed with brine, dried, concentrated under reduced pressure and recrystallized from a mixture of ethanol and water to give white crystals of 1-[4-(2-hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (0.70 g).

mp : 132-134°C

IR (Nujol) : 3505, 1605, 1300, 1280, 1235 cm^{-1}

NMR ($CDCl_3$, δ) : 1.46 (1H, br s), 2.92 (2H, t, J=6.5Hz), 3.89 (2H, br t, J=6.5Hz), 6.85 (1H, s), 7.23 (2H, d, J=8.7Hz), 7.29 (2H, d, J=8.7Hz), 7.44 (2H, d, J=8.4Hz), 7.91 (2H, d, J=8.4Hz)

MASS (m/z) : 411 (M+1)

Example 10

A solution of sodium nitrite (0.22 g) in water (5 ml) was added to an ice cooled mixture of 1-(4-chlorophenyl)-5-[4-(methylthio)phenyl]pyrazole-3-amine (0.82 g) and concentrated hydrochloric acid (3 ml). The mixture was stirred at 0°C for 30 minutes and added portionwise to a mixture of cuprous chloride (0.51 g) and concentrated hydrochloric acid (5 ml) at ambient temperature. The mixture was refluxed for 1 hour, and extracted with dichloromethane. The extract was washed with water, dried, and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel eluting with toluene to give crystals of 3-chloro-1-(4-chlorophenyl)-5-[4-(methylthio)phenyl]pyrazole (0.38 g).

NMR (DMSO-d_6, δ) : 2.47 (3H, s), 6.80 (1H, s), 7.17

(2H, d, J=8.7Hz), 7.26 (2H, d, J=8.7Hz), 7.32 (2H, d, J=8.8Hz), 7.51 (2H, d, J=8.8Hz)

MASS (m/z) : 335 (M+1)

Example 11

The following compounds described in (1) to (3) were obtained according to a similar manner to that of Example 10.

(1) 3-Chloro-5-[4-(methylthio)phenyl]-1-phenylpyrazole

NMR (DMSO-d_6, δ) : 2.46 (3H, s), 6.78 (1H, s), 7.15 (2H, d, J=8.7Hz), 7.23 (2H, d, J=8.7Hz), 7.24-7.31 (2H, m), 7.41-7.46 (3H, m)

MASS (m/z) : 301 (M+1)

(2) 3-Chloro-1-(4-fluorophenyl)-3-[4-(methylthio)phenyl]-pyrazole

NMR ($CDCl_3$, δ) : 2.48 (3H, s), 6.40 (1H, s), 7.03 (2H, t, J=9.1Hz), 7.09 (2H, d, J=8.7Hz), 7.17 (2H, d, J=8.7Hz), 7.26 (2H, dd, J=9.1, 4.8Hz)

MASS (m/z) : 319 (M+1)

(3) 3-Chloro-5-[4-(methylthio)phenyl]-1-(4-nitrophenyl)-pyrazole

mp : 195-197°C

IR (Nujol) : 1525, 1375, 1345 cm^{-1}

NMR ($CDCl_3$, δ) : 2.50 (3H, s), 6.46 (1H, s), 7.13 (2H, d, J=8.5Hz), 7.22 (2H, d, J=8.5Hz), 7.47 (2H, d, J=9.0Hz), 8.20 (2H, d, J=9.0Hz)

MASS (m/z) : 346 $(M+H)^+$

Example 12

A solution of m-chloroperbenzoic acid (0.49 g) in dichloromethane (10 ml) was added dropwise to a solution of 3-chloro-1-(4-chlorophenyl)-5-[4-(methylthio)phenyl]-

pyrazole (0.38 g) and stirred at ambient temperature for 1 hour. The mixture was washed with an aqueous solution of sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of toluene and ethyl acetate (50:1) to give crystals of 3-chloro-1-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole.

mp : 177-178°C

IR (Nujol) : 1310, 1140 cm^{-1}

NMR (DMSO-d_6, δ) : 3.25 (3H, s), 6.99 (1H, s), 7.35 (2H, d, J=8.8Hz), 7.53 (4H, d, J=8.7Hz), 7.94 (2H, d, J=8.5Hz)

MASS (m/z) : 367 (M+1)

Elemental Analysis Calcd. for $C_{16}H_{12}Cl_2N_2O_2S$:
C 52.33, H 3.29, N 7.63
Found : C 52.73, H 3.44, N 7.70

Example 13

The following compounds described in (1) to (3) were obtained according to a similar manner to that of Example 12.

(1) 3-Chloro-5-[4-(methylsulfonyl)phenyl]-1-phenylpyrazole

mp : 187-188°C

IR (Nujol) : 1600, 1310, 1150 cm^{-1}

NMR (DMSO-d_6, δ) : 3.23 (3H, s), 6.97 (1H, s), 7.29-7.35 (2H, m), 7.40-7.47 (3H, m), 7.50 (2H, d, J=8.5Hz), 7.90 (2H, d, J=8.5Hz)

MASS (m/z) : 333 (M+1)

Elemental Analysis Calcd. for $C_{16}H_{13}ClN_2O_2S$:
C 57.74, H 3.94, N 8.42
Found : C 57.81, H 3.90, N 8.05

(2) 3-Chloro-1-(4-fluorophenyl)-5-[4-(methylsulfonyl)-

phenyl]pyrazole
mp : 173°C
IR (Nujol) : 1600, 1310, 1150 cm^{-1}
NMR (DMSO-d_6, δ) : 3.24 (3H, s), 6.97 (1H, s), 7.30 (2H, t, J=9.2Hz), 7.40 (2H, dd, J=9.2, 5.1Hz), 7.51 (2H, d, J=8.6Hz), 7.92 (2H, d, J=8.6Hz)
MASS (m/z) : 351 (M+1)
Elemental Analysis Calcd. for $C_{16}H_{12}ClFN_2O_2S$:
C 54.78, H 3.45, N 7.99
Found : C 54.63, H 3.35, N 7.88

(3) 3-Chloro-5-[4-(methylsulfonyl)phenyl]-1-(4-nitrophenyl)pyrazole
mp : 189-191°C
IR (Nujol) : 1525, 1345, 1315, 1155 cm^{-1}
NMR ($CDCl_3$, δ) : 3.11 (3H, s), 6.59 (1H, s), 7.45 (2H, d, J=9.0Hz), 7.45 (2H, d, J=8.4Hz), 7.97 (2H, d, J=8.4Hz), 8.24 (2H, d, J=9.0Hz)
MASS (m/z) : 378 (M+1)
Elemental Analysis Calcd. for $C_{16}H_{12}ClN_3O_4S$:
C 50.93, H 3.18, N 11.14
Found : C 50.63, H 3.30, N 11.18

Example 14

A solution of m-chloroperbenzoic acid (0.68 g) in dichloromethane (5 ml) was added dropwise to an ice-salt cooled solution of 3-chloro-1-(4-fluorophenyl)-5-[4-(methylthio)phenyl]pyrazole (1.0 g), and stirred at 0°C for 40 minutes. The mixture was washed with an aqueous solution of sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of acetone and dichloromethane (1:10) to give amorphous powder of 3-chloro-1-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]pyrazole (0.25

g).

IR (Nujol) : 1510, 1050 cm^{-1}

NMR ($CDCl_3$, δ) : 2.75 (3H, s), 6.50 (1H, s), 7.05 (2H, t, J=9.0Hz), 7.25 (2H, dd, J=9.0, 4.8Hz), 7.36 (2H, d, J=8.6Hz), 7.62 (2H, d, J=8.6Hz)

MASS (m/z) : 335 (M+1)

Example 15

A solution of sodium nitrite (0.5 g) in water (5 ml) was added to the mixture of 4-[3-amino-5-[4-(methylthio) phenyl]pyrazol-1-yl]benzoic acid (1.5 g) in a solution of 20% hydrochloric acid (30 ml) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes and added portionwise to a mixture of cuprous chloride (1.0 g) and concentrated hydrochloric acid (10 ml). The mixture was refluxed for 2 hours and extracted with a mixture of ethyl acetate and tetrahydrofuran. The extract was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. A mixture of the residue in thionyl chloride (15 ml) was refluxed for 2 hours, and then concentrated under reduced pressure. The solution of the residue in tetrahydrofuran was added dropwise to a stirred mixture of ammonium hydroxide (28%, 5 ml) and tetrahydrofuran (20 ml) at 0°C, and the resulting mixture was stirred at the same temperature for one hour. The mixture was acidified with hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure.
A solution of phosphorus oxychloride (2.0 g) in N,N-dimethylformamide (10 ml) was stirred at 5°C for 30 minutes. To the solution was added a solution of the above residue in N,N-dimethylformamide, and stirred at 5°C for 2 hours. The reaction mixture was poured into ice-water and the resultant precipitate were collected. The precipitates were washed with water and dried. To the solution of the

precipitate in dichloromethane (50 ml) was added dropwise a solution of m-chloroperbenzoic acid (1.7 g) in dichloromethane (40 ml) at 5°C and stirred at ambient temperature for 1 hour. The resulting mixture was washed with an aqueous solution of sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and n-hexane (1:3) to give 3-chloro-1-(4-cyanophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole (155 mg).

mp : 160-165°C (decomp.)

IR (Nujol) : 2240, 1605, 1510, 1310, 1150 cm^{-1}

NMR ($CDCl_3$, δ) : 3.09 (3H, s), 6.56 (1H, s), 7.39 (2H, d, J=8.8Hz), 7.43 (2H, d, J=8.8Hz), 7.66 (2H, d, J=8.8Hz), 7.96 (2H, d, J=8.8Hz)

MASS (m/z) : 358 (M+1)

Example 16

To a mixture of (S)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (1.99 g) in dichloromethane (30 ml) was added borane-dimethyl sulfide complex (14.0 ml) under nitrogen atmosphere at room temperature and the resultant mixture was stirred for 1 hour. A solution of 1-(4-acetylphenyl)-3-difluoromethyl-5-[4-(methylthio)phenyl]-pyrazole (20.69 g) in dichloromethane (120 ml) was added dropwise to the mixture at -20°C. After standing overnight at 5°C, to the reaction mixture was added methanol (38.5 ml) and the resultant solution was concentrated under reduced pressure. Adding methanol (38.5 ml) followed by evaporation was repeated 3 times. And adding toluene (38.5 ml) followed by evaporation was also repeated 3 times. The resultant product was purified with column chromatography over silica gel eluting with dichloromethane followed with 10% ethyl acetate in dichloromethane and recrystallized from a mixture of ethanol and water (2:1) to give (+)-3-

difluoromethyl-1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylthio)phenyl]pyrazole (16.4 g).

mp : 59.67°C

IR (Nujol) : 3700-3100, 1600, 1342, 1162 cm^{-1}

NMR ($CDCl_3$, δ) : 1.50 (3H, d, J=6.5Hz), 1.91 (1H, d, J=3.7Hz), 2.48 (3H, s), 4.93 (1H, dq, J=6.5, 3.7Hz), 6.70 (1H, s), 6.76 (1H, dd, J=55.0Hz), 7.15 (2H, d, J=8.0Hz), 7.17 (2H, d, J=8.0Hz), 7.28 (2H, d, J=8.5Hz), 7.38 (2H, d, J=8.5Hz)

MASS (m/z) : 361 $(M+H)^+$

$[\alpha]_D^{27.9}$ = 13.38 (c=1.050, CH_3OH)

Example 17

To a mixture of (+)-3-difluoromethyl-1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylthio)phenyl]pyrazole (14.4 g), sodium bicarbonate (14.4 g), dichloromethane (100 ml) and water (160 ml) was added m-chloroperbenzoic acid (80%, 15.18 g) over a period of 15 minutes with vigorously stirring at 0°C. The resultant mixture was stirred for 1.5 hours at the same temperature. After adding water, the organic layer was separated washed with aqueous solution of sodium disulfite and sodium bicarbonate and with brine, and dried over magnesium sulfate. The resultant solution was concentrated under reduced pressure and recrystallized from ethanol (100 ml) to give (+)-3-difluoromethyl-1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]pyrazole (13.43 g).

mp : 149-150°C

IR (Nujol) : 3503, 1610, 1323, 1143 cm^{-1}

NMR (DMSO-d_6, δ) : 1.34 (3H, d, J=6.4Hz), 3.26 (3H, s), 4.77 (1H, qd, J=6.4, 4.4Hz), 5.30 (1H, d, J=4.4Hz), 7.11 (1H, s), 7.15 (1H, d, J=54.3Hz), 7.29 (2H, d, J=8.4Hz), 7.43 (2H, d, J=8.4Hz), 7.54 (2H, d, J=8.5Hz), 7.92 (2H, d, J=8.5Hz)

MASS (m/z) : 393 $(M+H)^+$

$[\alpha]_D^{28.7}$ = 11.78 (c=1.570, CH_3OH)

Example 18

The following compounds described in (1) to (3) were obtained according to a similar manner to that of Example 16.

(1) (-)-3-Difluoromethyl-1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylthio)phenyl]pyrazole
mp : 60-68°C
$[\alpha]_D^{27.6}$ = -12.95 (c=1.004, CH_3OH)

(2) (+)-1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole
NMR ($CDCl_3$, δ) : 1.49 (3H, d, J=6.5Hz), 2.48 (3H, s), 4.93 (1H, q, J=6.5Hz), 6.72 (1H, s), 7.12 (2H, d, J=8.8Hz), 7.17 (2H, d, J=8.8Hz), 7.29 (2H, d, J=8.6Hz), 7.38 (2H, d, J=8.6Hz)
$[\alpha]_D^{25}$ = 11.74 (c=2.535, CH_3OH)

(3) (-)-1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylthio)phenyl]-3-(trifluoromethyl)pyrazole
NMR ($CDCl_3$, δ) : 1.49 (3H, d, J=6.4Hz), 2.48 (3H, s), 4.93 (1H, q, J=6.4Hz), 6.72 (2H, s), 7.12 (2H, d, J=8.8Hz), 7.17 (2H, d, J=8.8Hz), 7.29 (2H, d, J=8.6Hz), 7.38 (2H, d, J=8.6Hz)
$[\alpha]_D^{26}$ = -7.22 (c=1.89, CH_3OH)

Example 19

The following compounds described in (1) to (3) were prepared according to a similar manner to that of Example 17.

(1) (-)-3-Difluoromethyl-1-[4-(1-hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 150-151°C

IR (Nujol) : 3510, 1610, 1325, 1148 cm^{-1}

NMR ($CDCl_3$, δ) : 1.51 (1H, d, J=6.5Hz), 1.97 (1H, d, J=3.6Hz), 3.08 (3H, s), 4.96 (1H, qd, J=6.4, 3.6Hz), 6.78 (1H, dd, J=54.8Hz), 6.83 (1H, s), 7.25 (1H, d, J=7.4Hz), 7.41 (1H, d, J=7.4Hz), 7.44 (2H, d, J=8.5Hz), 7.90 (2H, d, J=8.5Hz)

MASS (m/z) : 393 $(M+H)^+$

$[\alpha]_D^{28.7}$ = -12.24 (c=1.103, CH_3OH)

(2) (+)-1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole

mp : 120-121°C

NMR ($CDCl_3$, δ) : 1.50 (3H, d, J=6.5Hz), 1.95 (1H, d, J=3.7Hz), 3.08 (3H, s), 4.96 (1H, qd, J=6.5, 3.7Hz), 6.85 (1H, s), 7.27 (2H, d, J=8.45Hz), 7.42 (2H, d, J=8.5Hz), 7.44 (2H, d, J=8.3Hz), 7.91 (2H, d, J=8.3Hz)

MASS (m/z) : 411 $(M+H)^+$

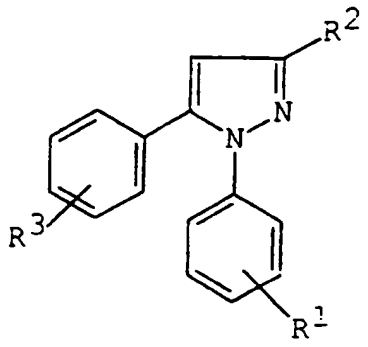
$[\alpha]_D^{28}$ = 8.5 (c=1.000, EtOH)

(3) (-)-1-[4-(1-Hydroxyethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole

mp : 124-129°C

C L A I M S

1. A compound of the formula :



[I]

wherein R^1 is hydroxyethyl, 1-hydroxy-1-methylethyl, hydrogen, halogen, nitro, or cyano,
R^2 is chloro, cyano, or lower alkyl optionally substituted with halogen, and
R^3 is lower alkylthio, lower alkylsulfinyl, or lower alkylsulfonyl,
provided that when R^1 is hydrogen, halogen, nitro, or cyano,
then R^2 is chloro,
and a pharmaceutically acceptable salt thereof.

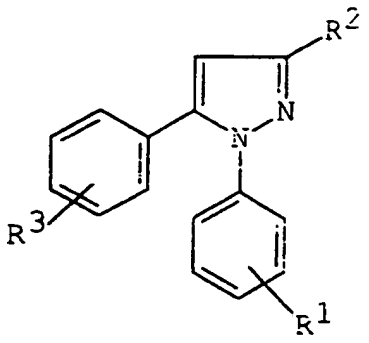
2. The compound according to claim 1,
wherein R^1 is hydroxyethyl or 1-hydroxy-1-methylethyl,
R^2 is cyano or lower alkyl optionally substituted with halogen, and
R^3 is lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl.

3. The compound according to claim 1,

wherein R^1 is hydrogen, halogen, nitro or cyano,
R^2 is chloro, and
R^3 is lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl.

4. The compound according to claim 3, wherein R^1 is hydrogen or halogen.

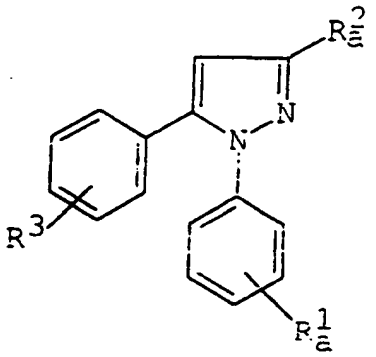
5. A process for preparing a compound of the formula :



[I]

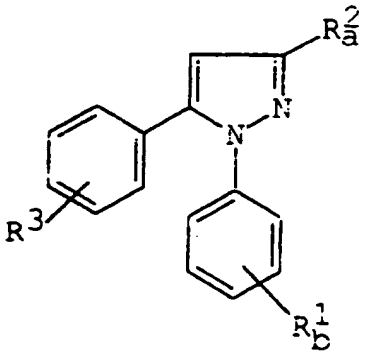
wherein R^1 is hydroxyethyl, 1-hydroxy-1-methylethyl, hydrogen, halogen, nitro, or cyano,
R^2 is chloro, cyano, or lower alkyl optionally substituted with halogen, and
R^3 is lower alkylthio, lower alkylsulfinyl, or lower alkylsulfonyl,
provided that when R^1 is hydrogen, halogen, nitro, or cyano,
then R^2 is chloro,
or a salt thereof,
which comprises,

a) reducing a compound of the formula :



[II]

wherein R^3 is as defined above,
R^1_a is acetyl, and
R^2_a is cyano or lower alkyl optionally substituted with halogen,
or a salt thereof,
to give a compound of the formula :

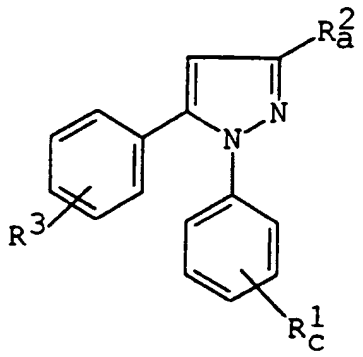


[Ia]

wherein R^2_a and R^3 are each as defined above, and
R^1_b is 1-hydroxyethyl,

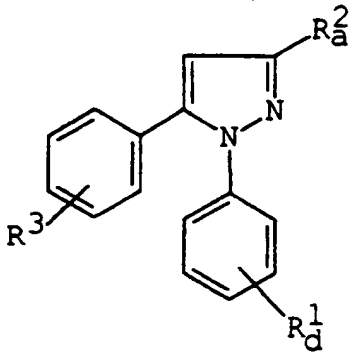
or a salt thereof,

b) subjecting a compound of the formula :



[III]

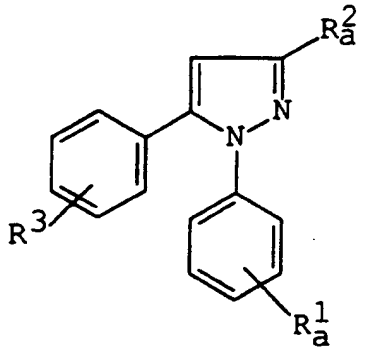
wherein R^2_a and R^3 are each as defined above and
R^1_c is carboxy,
or its reactive derivative at the carboxy group,
or a salt thereof,
to alkylation to give a compound of the formula :



[Ib]

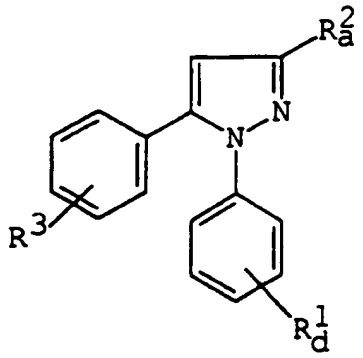
wherein R_a^2 and R^3 are each as defined above and
R_d^1 is 1-hydroxy-1-methylethyl,
or a salt thereof

c) subjecting a compound of the formula :



[II]

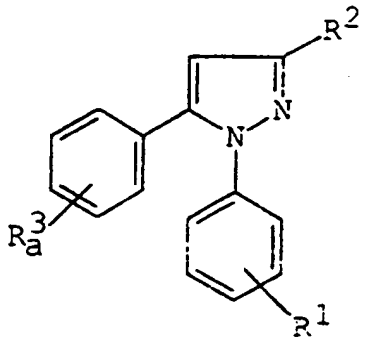
wherein R_a^1, R_a^2 and R^3 are each as defined above,
or a salt thereof,
to alkylation at the acetyl group to give a compound of the formula :



[Ic]

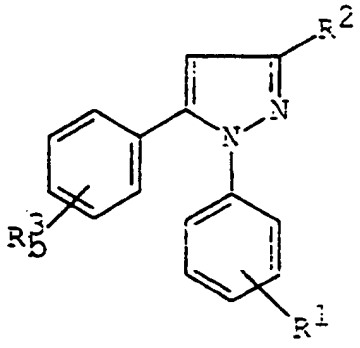
wherein R^1_a, R^2_a and R^3 are each as defined above, or a salt thereof,

d) oxidizing a compound of the formula :



[Id]

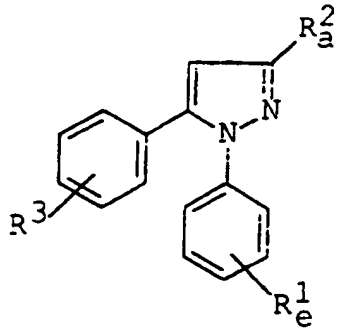
wherein R^1 and R^2 are each as defined above and R^3_a is lower alkylthio,
or a salt thereof,
to give a compound of the formula :



[Ie]

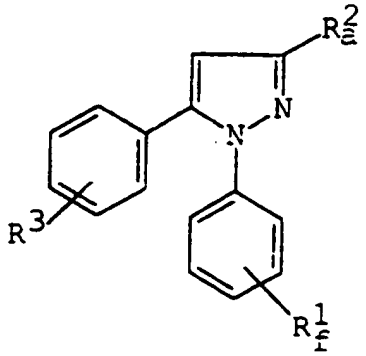
wherein R^1 and R^2 are each as defined above and
R^3_b is lower alkylsulfinyl or lower alkylsulfonyl,
or a salt thereof

e) reducing a compound of the formula :



[IV]

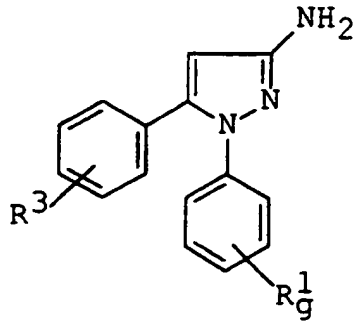
wherein R^2_a and R^3 are each as defined above and
R^1_e is carboxymethyl,
or its reactive derivative at the carboxy group,
or a salt thereof,
to give a compound of the formula :



[If]

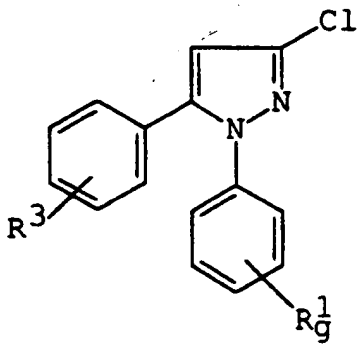
wherein R^2_a and R^3 are each as defined above and
R^1_f is 2-hydroxyethyl,
or a salt thereof, or

f) subjecting a compound of the formula :



[V]

wherein R^3 is as defined above and
R^1_g is hydrogen, halogen, nitro or cyano,
or a salt thereof,
to chlorination to give a compound of the formula :



[Ig]

wherein R_g^1 and R^3 are each as defined above, or a salt thereof.

6. A pharmaceutical composition comprising the compound of claim 1, as an active ingredient, in association with a pharmaceutically non-toxic carrier or excipient.

7. A compound of claim 1 for use as a medicament.

8. COX-II inhibiting agent comprising the compound of claim 1.

9. A method for the treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases which comprises administering an effective amount of the compound of claim 1 to human beings or animals.

10. Use of the compound of claim 1 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases in human beings or animals.

INTERNATIONAL SEARCH REPORT

Interr ul Application No
PCT/JP 96/02919

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D231/12 C07D231/14 A61K31/415 C07D231/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,95 15316 (G. D. SEARLE & CO.) 8 June 1995 cited in the application see claims 1,19,37	1-10
X	EP,A,0 418 845 (FUJISAWA PHARMACEUTICAL CO., LTD.) 27 March 1991 cited in the application see claims 1,8-11	1-10
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P,X	US,A,5 521 207 (G. D. SEARLE & CO.) 28 May 1996 see claims 1-3	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 December 1996	17 -01- 1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Herz, C

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INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/JP 96/02919

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO,A,95 15318 (G. D. SEARLE & CO.) 8 June 1995 cited in the application see claims 1,9,17	1-10

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